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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/879,320	06/12/2001	Ajay Hasmukhlal Upadhyay	RD 01022	5176

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EXAMINER	
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ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/879,320	UPADHYAY, AJAY HASMUKHLAL	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11-5-09*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,8,33,34 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,8,33,34 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of amendment and remarks dated 11-5-09 is acknowledged.

Claims 2-4, 8, 33, 34 and 37 are pending.

The following rejection of record has been maintained:

Claim Rejections - 35 USC § 103

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 2-4, 8, 33, 34 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,372,252 to Blume et al (Blume) in view of US 5,032,406 to Dansereau et al (Dansereau), US 3,627,583 to Troy et al and US 6,623,756 to Wilber et al (Wilber) or US 6,372,252 to Blume et al (Blume) in view of US 5,032,406 to Dansereau et al (Dansereau) and US 6,623,756 to Wilber et al (Wilber.

Blume teaches immediate and sustained release formulations comprising guaifenesin. Blume teaches loading guaifenesin and methocel into a high shear mixer, mixed at high speed, adding water and further mixing at additional time to complete granulation. The composition is next dried in fluid dryer and then passed through a mill fitted a suitable size screen (col. 7, lines 63 through col. 8, lines 23). Thus, the resulting material of Blume reads on agglomerated mixture because the processing of the material involves the same steps as described in the instant application.

Blume fails to teach granulation of guaifenesin with polyvinylpyrrolidone.

Dansereau teaches a tablet composition that provides dual action, for immediate and sustained release, comprising an outer tablet and an inner tablet respectively. The

active ingredient of both inner and outer tablets comprises guaifenesin. The inner tablet particularly comprises guaifenesin and polyvinylpyrrolidone (PVP) (example I). Dansereau teaches that the inner tablet is made as follows (col. 6):

> The inner tablet is made by oscillating guaifenesin and half of the polyvinylpyrrolidone through a 30 mesh screen. The blend is then transferred to a pharmaceutical grade blender and mixed until it is of uniform consistency. It is then granulated with polyvinylpyrrolidone that had been previously dissolved in a sufficient amount of purified water to make a solution of from about 8% to about 12% of polyvinylpyrrolidone. This mixture is discharged and dried in a forced air oven at 40° C. until the water content is less than 1%. The dried granulation is then oscillated through a 12 mesh screen and returned to the blender. The remaining polyvinylpyrrolidone, microcrystalline cellulose and talc are added to this dried granulation and mixed until it is of uniform consistency. Finally, zinc stearate is added and the mixture is mixed until it is of uniform consistency. This mixture is then compressed into inner tablets using a standard tableting press.

Thus, the resulting inner tablet composition of Dansereau read on the claimed agglomerate mixture because the process involves the same steps as described in the instant specification (page 3, lines 15-20). Dansereau fails to teach the claimed particle sizes.

Wilber teaches tablets for controlled release of a desired drug that are directly compressed from a flowable, compressible mixture of the drug and a rheology modifying polymer or a copolymer and additional excipients (abstract). The rheology modifier is a homopolymer or copolymer is processed into a desirable granular size by

compacting into large agglomerates or aggregates and subsequently fractured into smaller granules and screened to suitable particle size of low amounts of dust, such that the flow characteristics and compressibility are good and the tablets are directly compressed (col. 4, L 44-48). Wilber teaches that the particle size of the granulated polymers is generally falls through 40-45 mesh but retained on 150 or 200 mesh (col. 4, l 44-67). When converted the 40-45 mesh equals 420 microns and 150-200 mesh size equals 75-100 microns. Thus the particle size ranges between 75-420 microns and overlaps with instant 45-425.Wilber also teaches that the over sized particles should be 5% or less and under sized particles should be 25% or less (lines bridging col. 4-5). Wilber teaches that the resulting optimum sized particles obtained are free flowing and are suitable for direct compression. The exemplified compositions of Wilber teach flow rates and compressibility values such as in examples 1-3. Wilber teaches a number of pharmaceutical agents that may be suitable for compressing in to tablets including guaifenesin (col. 6, L 54) but does exemplify guaifenesin.

Troy teaches tablets formed by direct compression from a mixture of an active material such as therapeutic material and as a direct compression vehicle dry, free-flowing, granular sugar and a binder (abstract). Troy teaches that in order to obtain free-flowing particles of 12 mesh to 325 mesh (col. 1, L 50-65). Troy states that tablets result in good physical properties and readily dissolve in aqueous media (col. 1 and col. 4, L 1-10). Troy suggests mixing sugar and the binder to effect agglomeration of about 325 mesh (44 microns according to the declaration submitted by applicants on 10-26-07) but

not greater than 12 mesh (col. 3, L 7-15 and lines 46-61). Among the active agents, Troy suggests antitussives but does not explicitly state employing guaifenesin.

It would have been obvious for one of an ordinary skill in the art at the time of the instant invention from the teachings of Troy and Wilbur that particle sizes between 12-325 or 20-200 respectively, are important for free flowing and the ability for compression such that the drug is released at a determined rate from the compressed tablet. Troy teaches that too fine a powder causes capping and while sizing of the granules particles is important for free flowing of drug. Wilbur suggests the allowed amounts of fines and oversized particle within which the tablets can be easily compressed. Troy as well as Dansereau recognizes PVP as a suitable binder for compressible tablets, particularly guaifenesin (Dansereau). Accordingly, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention was made to employ PVP for the processing and preparation of compressible guaifenesin tablets of Blume because Troy as well as Dansereau recognize PVP as a suitable binder and Dansereau recognizes methylcellulose (Blume) and PVP as equivalent binders as well as disintegrants in preparing a sustained release compressible tablet preparation comprising guaifenesin.

With respect to the claimed particle sizes, Blume teaches that no more than 30% granulation material passes through 100 mesh (150 microns) and not more than 10% retained on 10-mesh screen (greater than 850 microns). Thus, majority of the particles of Blume are in the range of 150 microns – 2 mm and a smaller percentage of particles are below 150 microns. A maximum of 30% of the particles that pass through the 100-

mesh screen, according to Blume, could be any size below 150 microns (as low as 45 microns claimed in the instant invention). While Blume does not teach the exact percentages of particle sizes claimed in the instant application, there is an overlap in the particle sizes between instant application and that of Blume (150 nm to 425 nm). On the other hand, Wilbur suggests free flowing particles of appropriate size (not too fine a powder or not too oversized) are easy to compress and Troy suggests a particle size of 12 mesh (1.41 mm) to 325 mesh (44 microns) as suitable for free flowing, stable and compressible tablets. Accordingly, a skilled artisan would have readily optimized the particle sizes of the granulated PVP and guaifenesin between 12 mesh and 325 mesh sizes such that the particles have an optimum flow rate, strength and stability and yet do not show capping.

For the claimed additives such as glidants, lubricants, silica, stearic acid etc., Blume and Dansereau teach the conventional excipients including lubricants such as magnesium stearate, calcium stearate etc; binders such as povidone (polyvinylpyrrolidone), gelatin, starch; glidants such as talc or silicon dioxide, stabilizers and other excipients such as lactose, sorbitol etc. Accordingly, in the absence of evidence to the criticality of the specific excipients and their amounts (claims 3-4 & 33-34), it would have been obvious for one of an ordinary skill in the art at the time of the instant invention was made to the choose the appropriate excipient and optimize the amounts of the same in the composition of Blume with an expectation to obtain compressed tablets of desired compressibility or hardness and very less friability because the cited prior art desires the same features.

Response to Arguments

2. Applicant's arguments filed 11-5-09 have been fully considered but they are not persuasive.

3. Applicants argue that the four references cited in the rejection do not contain all of the recited limitations of the instant application. It is argued that the examiner overstates the teachings of the references to meet the claimed limitations. It is argued that Blume does not contain other recited elements such as PVP binder , solubilizer and/or disintegrant in claimed amounts. It is argued that only the claimed limitations can produce a tablet under relatively low pressure (not more than 2.5 tons), which exhibits less than 1% friability, hardness in the range of 10.3 to 17.0 kp and is resistant to capping. It is argued that Blume specifically teaches that his granulation far exceeds the maximum particle size permitted. It is argued that the teaching of Blume that the resulting formulation "may further be compressed on a table compressing machine using tooling to form tablets (column 8, lines 36-37)", does not contain any disclosure of the pressure of the tabletting press, nor of the resulting tablet hardness, capping and friability can be found in Blume.

4. Applicanst' argue that examiner's attempt to cobble together the teachings of Dansereau and Troy do not establish prima facie case of obviousness. It is argued that Wilbur reference does not teach agglomerates of instant size and instead teaches the particle size of the rheology modifying agent and further suggests that the particulate rheology modifying agents may be mixed with active agents (of no specified particle

sizes) as well as more excipients mixed in any conventional manner to produce a blend. It is argued that the reference fails to teach particulate guaifenesin and that when the Patentee does describe the blending of the guaifenesin and binder: his disclosure is fatally defective as to the particle size of any resulting agglomeration of guaifenesin and binder, is silent as to the parameters upon which the tableting press operates and clearly does not specify the conditions recited in the claims and is similarly silent as to the properties of the resulting tablet.

5. Applicants' arguments are not persuasive because it appears from the arguments presented above that the arguments are based on the premise that each and every reference cited should teach all of the claimed limitations. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The rejection of record explained the deficiencies of each of the cited references. All of the cited prior art pertains t the field of tablet making by granulation and compression.

6. The combination of guaifenesin and polyvinylpyrrolidone is clearly taught by Dansereau et al reference, which also teaches the two are blended, granulated and passed to a mesh of specific screen size (though not of the same size as claimed in the instant claims). Thus, granulating PVP and guaifenesin together and screening for desired particle sizes is not unknown according to Dansereau et al reference. Blume also teaches blending the claimed drug with a hydrophilic polymer, granulating and

screening (col. 4, L 4-15). While the examiner agrees that Wilbur only teaches particle sizes of the rheology modifying polymer and not of the drug, a skilled artisan provided with the disclosure of Blume et al and Dansereau et al would look to other teachings in the prior art for compression of tablets. A skilled artisan would envisage blending of rheology modifier of Wilbur or binder of Troy with the active agent (guaifenesin) before the formation of agglomerates and the screening process, with an expectation to achieve good compression and controlled release of the drug and good physical properties without the problems of capping etc. Wilbur also teaches that a granular tabletting mixture is formed by blending granular said polymer and an active agent and compressed to form a tablet. While Wilbur states that the active need not be granulated, when one used granulated slightly crosslinked rheology modifying polymer (col. 8, l 5-10), this does not constitute a teaching away from granulating the active, particularly in light of the teachings of Dansereau and also Blume (fig. 2). Thus a skilled artisan would have employed the particle sizes taught by Troy and/or Wilbur in preparing the granulated agglomerates of guaifenesin 9Blume or Dansereau) and PVP (Dansereau) in addition to the other excipients. In this regard, Fig,2 of Blume teaches not only drug but also additional materials such as methocel, carbopol, magnesium stearate, colorant etc., to achieve the advantages suggested by Wilbur and Troy. In response to applicant's, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one

of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

7. With respect to the results in tables 2A-2G, it is observed that while compositions of the instant invention do not exhibit capping at any compression force applied, comparative examples 1 and 3 also do not exhibit capping at the highest compression force. For the friability, comparative examples do provide low friability (<1%0 even at highest force applied. Thus, it is not clear if the instant compositions provide any unexpected advantage over the comparative compositions.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -5.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611
January 19, 2010